

The State of Electronic Submissions at CDER

Virginia Hussong

Data Management Solutions Team
Division of Data Management Services
and Solutions
(FDA/CDER/OPI/OBI)

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Team Info

Data Management Solutions

eSUB Team
esub@fda.hhs.gov

- General help with electronic submissions
- Liaison with division/sponsor to solve problems, facilitate communication
- Analyze your sample eCTD
- Train reviewers in review tools
- Special projects – e.g., Module 1 update, eCTD v.4 implementation

eDATA Team
edata@fda.hhs.gov

- Help with standardized and legacy data submissions
- Validate, load, troubleshoot datasets
- Analyze your sample SDTM
- Train reviewers in JMP
- Special projects – e.g., data rating system, data versioning, other research



Submission Metrics





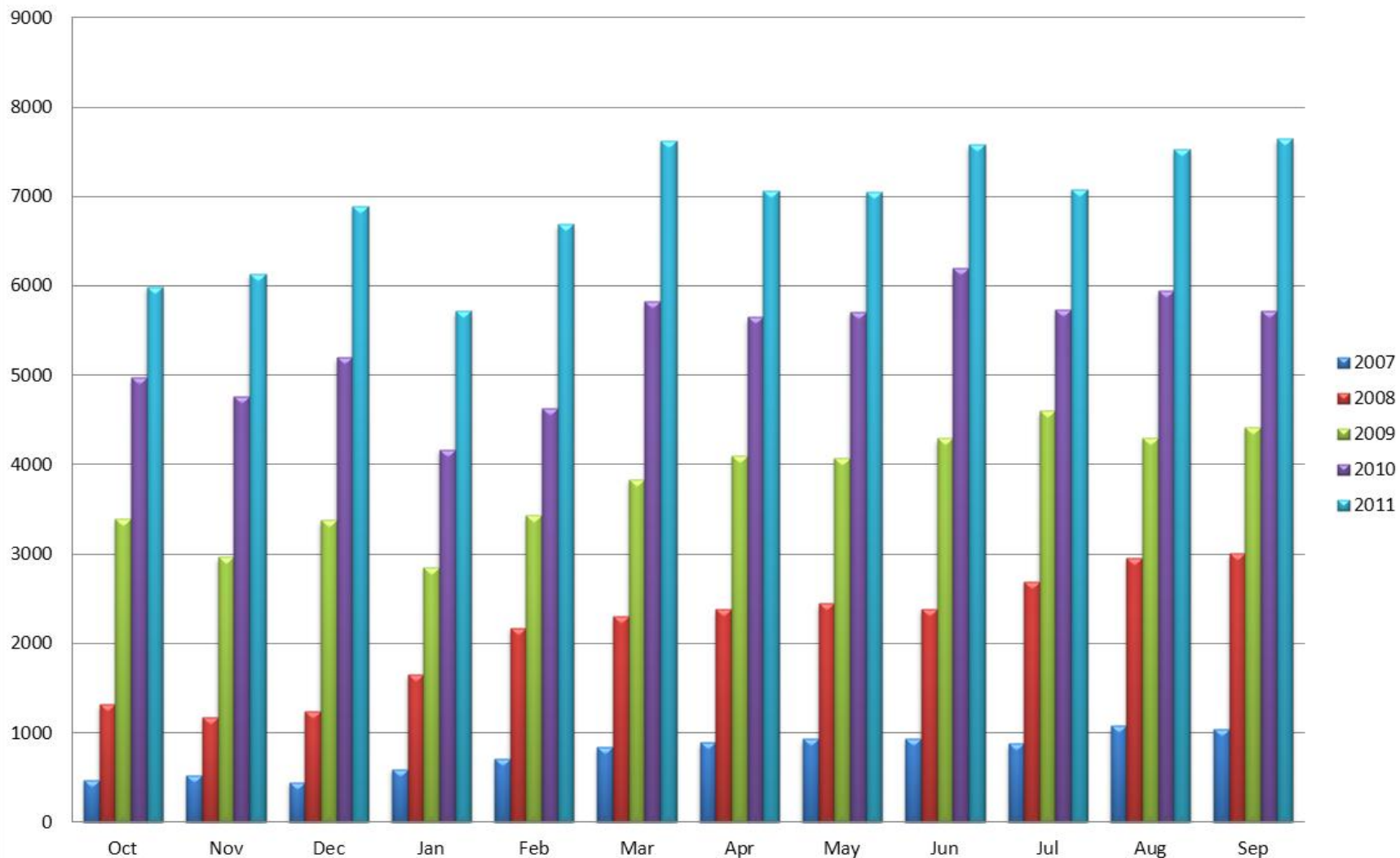
eCTD Submissions

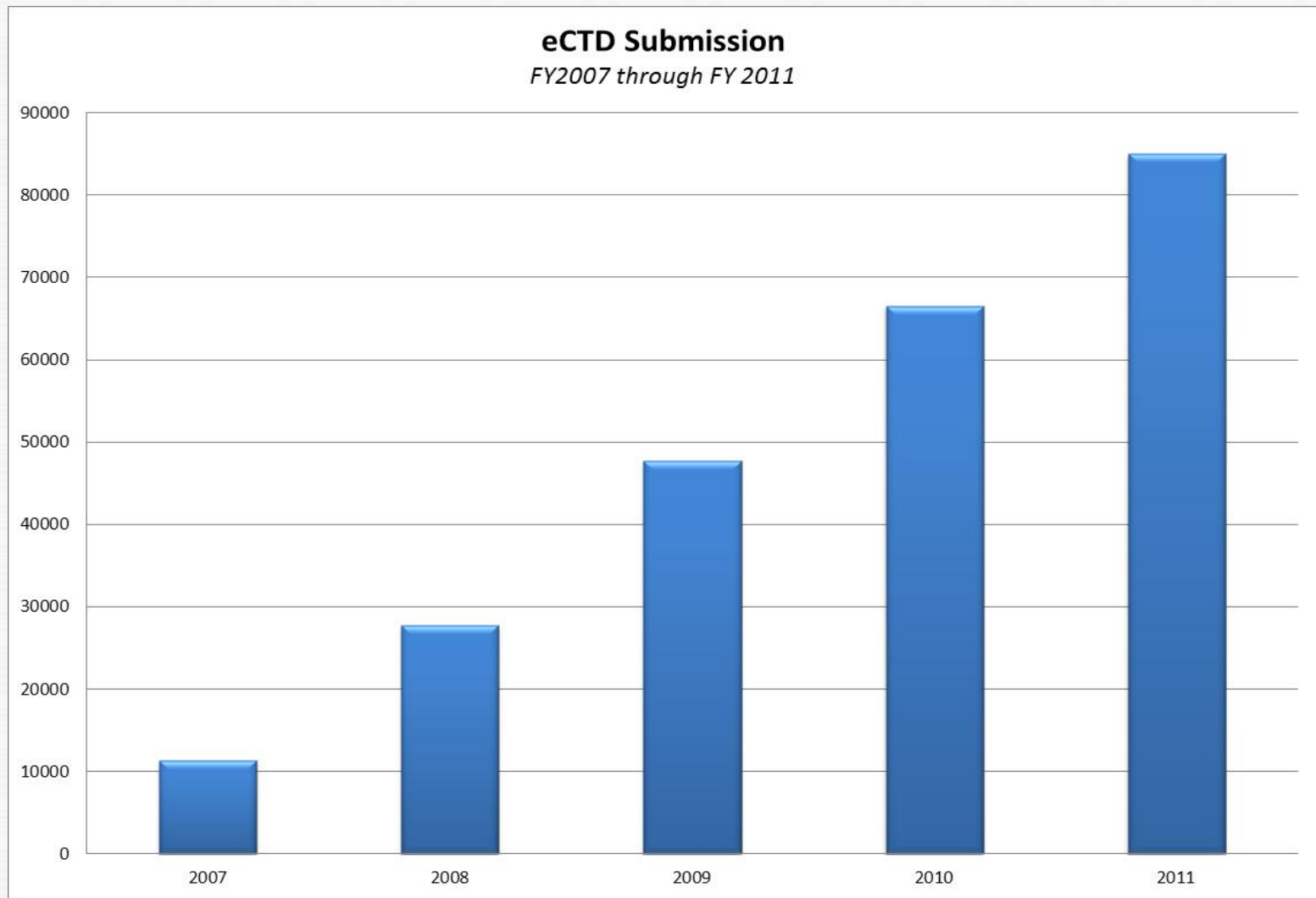
as of May 1, 2012

Application	No. of Applications	No. of Sequences
IND	4,388	167,798
NDA	2,144	61,017
ANDA	6,667	52,501
BLA	225	18,262
MF	1,137	5,213
OTHER	809	1,492
Total	15,380	306,282



eCTD Submission FY2007 through FY 2011





CDER Investigational New Drugs

	FY2007	FY2008	FY2009	FY2010	FY2011	FY2012*
IND Research	13,236	11,833	12,863	14,816	16,039	7,377
IND Commercial	74,898	73,784	74,163	77,402	77,013	37,634
IND Total	88,134	85,617	87,026	92,218	93,052	45,011
IND Research Electronic	114	307	456	721	1,185	640
IND Commercial Electronic	6,960	13,006	24,913	36,794	48,116	26,079
IND Electronic Total	7,074	13,313	25,369	37,515	49,301	26,719
IND Electronic %	8.03%	15.55%	29.15%	40.68%	52.98%	59.36
IND Research eCTD	66	217	326	595	1,008	570
IND Commercial eCTD	5,525	12,338	24,448	36,219	47,564	25,865
IND eCTD	5,591	12,555	24,774	36,814	48,572	26,435
eCTD % of Total	6.34%	14.66%	28.47%	39.92%	52.20%	58.73%
eCTD % of Electronic	79.04%	94.31%	97.66%	98.13%	98.52%	98.93%

* Through 3/31/12



CDER New Drug Applications

Original, Supplement, Miscellaneous

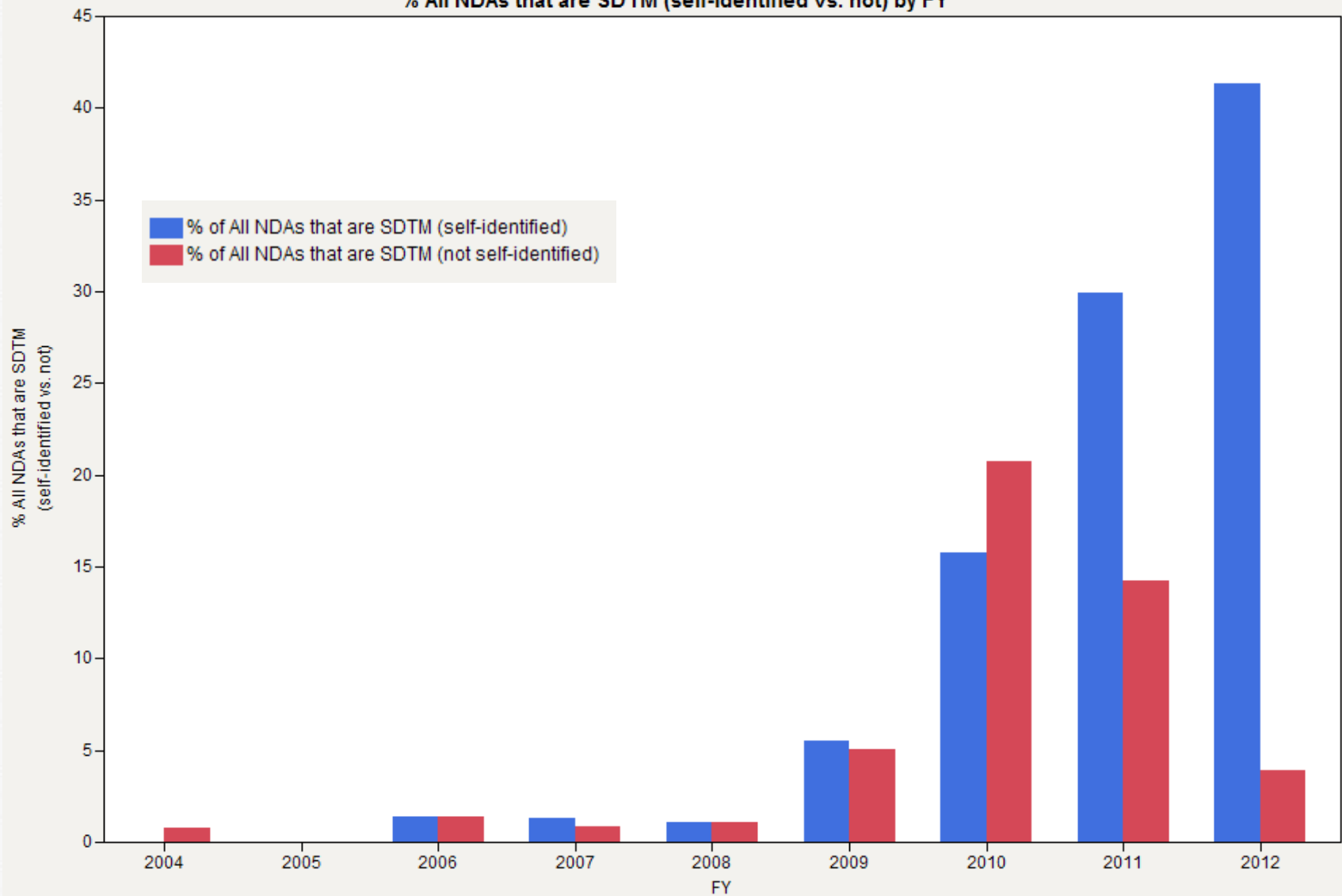
	FY2007	FY2008	FY2009	FY2010	FY2011	FY2012*
NDA Total	23,310	22,308	22,148	22,443	23,254	12,458
NDA Electronic	8,771	11,272	13,297	15,497	17,396	9,704
NDA Electronic %	37.63%	50.53%	60.04%	69.05%	74.81%	77.89%
NDA eCTD	2,085	7,410	11,146	14,007	15,937	9,170
NDA eCTD % of Total	8.94%	33.22%	50.33%	62.41%	68.53%	73.61%
NDA eCTD % of Electronic	23.77%	65.74%	83.82%	90.39%	91.61%	94.50%

* Through 3/31/12





% All NDAs that are SDTM (self-identified vs. not) by FY





Rejections

- When?
 - Upon receipt and during processing at CDER
- Why?
 - Can't read, load or archive your submission
- How?
 - We send a message to your WebTrader inbox
 - If you sent on physical media, we send a fax
- *Note: Rejection is not “Refuse to File”*





What Commonly Gets Rejected?

- Duplicate submissions

~ 50% of rejections are duplicate submissions

- Invalid submission number or type
- High-level validation errors
- Single file submissions
- How often?

~1% of submissions are rejected

(current averages are 10,000 submissions per month, 100 rejected)





Allowed File Types

- PDF v. 1.4 – 1.7 for documents (*Word allowed for labeling negotiations and OGD submissions*)
- SAS XPT v. 5 for data (not Excel)
- Can't read images such as DICOM
- Do not send .exe files
- File types for OPDP submissions in Module 1 will be expanded



Tools and Versions in Use

- Global Submit Review and Validate v. 4
- Submit in Adobe PDF v. 1.4 – 1.7

Data:

- Submit in SAS XPORT v. 5
- JMP v. 9.0.2 (used by majority of non-statistician reviewers)
- JMP Clinical (runs on JMP 9)
- JReview v. 9.2.3
- WebSDM
- SAS 9.2
- OpenCDISC v. 1.2

Other:

- Microsoft Office 2003 (mostly) and 2010 (only on newer machines)
- Adobe Acrobat 8



Transmission Formats

- ESG (preferred)
- USB devices (for larger submissions)
- Tape formats will be retired 12/31/2012
- CD/DVD still accepted
- See Transmission Specification:

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163567.pdf>





Reminder: Form 3674



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

**Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with
Requirements of ClinicalTrials.gov Data Bank (42 U.S.C. § 282(j))**

(For submission with an application/submission, including amendments, supplements, and resubmissions, under §§ 505, 515, 520(m), or 510(k) of the Federal Food, Drug, and Cosmetic Act or § 351 of the Public Health Service Act.)

- FDA's Office of Policy would like you to know:
 - Form 3674 is important and needs to be submitted *
 - Required by FDAAA since 2007
 - See <http://www.fda.gov/RegulatoryInformation/Guidances/ucm125335.htm>
 - New INDs, NDAs, BLAs
 - New Clinical Protocol Submissions to an IND
 - New Efficacy Supplements (to NDAs & BLAs)
 - ANDAs
 - FDA form 3674 belongs as a separate document in the Cover Letters section, 1.2. The leaf title should be "FDA form 3674"

** list only includes applications/submission types relevant to CDER*



Current Projects

- Update of eCTD Module 1
- Implement new eCTD validation codes and new viewer/validation software
- Automated Validation and Loading of Study Data
 - Includes versioning of data
 - Important info about large submission sizes
- Regulated Product Submission (RPS) – eCTD v. 4





Update of eCTD Module 1

- Reorganizes and updates Administrative Information
- Allows CDER OPDP (formerly DDMAC) to accept eCTD submissions
- Allows ability to apply one submission to multiple applications (e.g., bundled supplement)
- Table of Contents updates/enhancements
- Consistent with the upcoming RPS Standard (eCTD v. 4)





Module 1 Schedule

- Publish final documentation (July or August)
 - eCTD Backbone Files Specification for Module 1
 - US regional DTD
 - FDA eCTD Table of Contents Headings and Hierarchy
- Public Meeting
 - September 18, 2012, 8–11:30am at White Oak
 - Address industry comments and answer questions
- eCTD Guidance Updates (by 12/31/2012)
- Update other documents (Validation Criteria, Transmission Specifications to include new file types)
- Implement new software & begin receiving submissions





New Validation Codes and Software Update

- Validation Criteria 2.1
- Global Submit 2010
- Valid Values 3.0 will be supported
- Current estimated date: January 2013
- 30 days notice will be given prior to implementation
- Notice posted on the Validation web page:
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm163181.htm>





Automated Validation & Loading of Study Data

- Automates loading, validation of study data into a single repository for downstream uses
- Eliminates manual copying of study data by Reviewers, tools, and CDER OBI eDATA Review Team to many staging areas
- Performs revision control for study data by submission and study ID
- Provides a single and consistent view of many versions of studies to medical and statistical reviewers, and notification when new data is uploaded
- Allows existing COTS tools (e.g., JMP) to access the up-to-date study data thus facilitate correct reviews of sponsors' submissions
- Scope: all data received, including SDTM, SEND, ADaM





Large Submission Sizes

- Coincide with submission of SDTM
 - *But that's OK – we want SDTM!!*
- Take a long time to transmit via ESG
- Take a long time to copy from physical media
- Recent examples: 240 & 255 GB original NDA submissions





Solution

- Re-size your SAS XPT v.5 data files
- Remove excess space in columns
- Reductions of 70% on average are achieved (tested by FDA and industry)
- Instructions available from eDATA@fda.hhs.gov or eSUB@fda.hhs.gov





Recent examples:

240GB & 255GB original NDA submissions

Sponsor followed the resizing method to achieve
140GB & 130GB final sizes!

Reduced
to only the width
needed



Variable Name	Variable Type	Previous Variable Length	Modified Variable Length
DOMAIN	Character	2	2
LBBFL	Character	2	2
LBCAT	Character	200	20
LBDTC	Character	50	20
LBNRIND	Character	8	8
LBORNRHI	Character	200	10
LBORNRLO	Character	200	10
LBORRES	Character	200	15
LBORRESU	Character	200	10



eCTD v4 (RPS) ICH Schedule

- Post Draft eCTD v4 ICH v1 Implementation Guide and Draft Regional Module 1 Implementation Guides (June/July 2012)
- Finalize test cases (June 2012 – September 2012)
- ICH Testing (Oct 2012 – Aug 2013)
- HL7 Normative Ballot (Sept 2013)
- Update/Finalize Implementation Guides (June 2013 – Nov 2013)
- ICH Comment & Reconciliation (Dec 2013 – June 2014)



Contact Info

- Virginia.Hussong@fda.hhs.gov
- 301-796-1016
- ESUB@fda.hhs.gov
- EDATA@fda.hhs.gov

